

Steen Boesby

**SOME ASPECTS OF
GASTRO-OESOPHAGEAL REFLUX**



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Bekendtgørelse

I undervisningsministeriets bekendtgørelse af 31. januar 1977 om erhvervelse af doktorgraden § 19 er der bl.a. fastsat følgende bestemmelser om det offentlige forsvar af doktorafhandlinger:

Stk. 1. Forsvarshandlingen er offentlig og ledes af formanden for det kollegiale organ, som sagen hører under, eller en anden videnskabelig medarbejder eller lærer, som formanden har udpeget dertil.

Stk. 3. Eventuelle uofficielle opponenter må melde sig til den, der leder forsvarshandlingen, inden handlingens begyndelse. Lederen af forsvarshandlingen kan dog lade senere anmeldte opponenter få ordet, men uden at fratage tidligere anmeldte opponenter deres forrettigheder.

Stk. 4. Hvis doktoranden ønsker det, kan der gives ham ret til at indlede forsvarshandlingen med en forelæsning af indtil $\frac{1}{2}$ times varighed, hvori der gives en oversigt over afhandlingens emne og de forskningsresultater, der er fremlagt til bedømmelse.

Stk. 5. Der gives i almindelighed hver af de officielle opponenter højst $1\frac{1}{2}$ time og hver uofficiel højst $\frac{3}{4}$ time, heri indbefattet den tid, doktoranden behøver til at give svar. Den tid, der gives opponenterne, kan dog efter omstændighederne indskrænkes eller udvides. Hele forsvarshandlingen må højst vare 6 timer.

Stk. 6. Forsvarshandlingen skal foregå på dansk, norsk eller svensk, medmindre der af det kollegiale organ gives tilladelse til at anvende et andet sprog.

Odense universitet, den 1. juni 1977.

Steen Boesby

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PREFACE

The present study was undertaken in the period 1973 to 1976 during my employment as a clinical assistant at the Inst. of Surgery, Odense University Hospital. The investigations were made at the Dept. of Thoracic and Cardiovascular Surgery, under the supervision of the head of department, Professor, dr.med. H. Rahbek Sørensen, who encouraged me to carry out the investigations, provided me with favourable working conditions and followed my work with the greatest interest.

The many technical problems were solved owing to the great personal effort of Mr. Tommy Madsen, medical engineer.

Dr.med. Svend Arne Pedersen introduced me to the various problems and taught me the techniques of pressure recording as well as making valuable contributions to the discussion of my results.

Dr.med. C.M. Madsen and Dr.med. F. Truelsen, Dept. of Surgical Gastroenterology and Dr.med. I.L. Marner, Dept. of Medical Gastroenterology, kindly placed enough confidence in me to let me examine their patients.

Cand.scient., Mrs. Lise Hansen was of great help to me in the solving of statistical problems.

Apart from the persons mentioned above as well as the other staff members of the Dept. of Thoracic and Cardiovascular Surgery, many people have supported this work in various ways at its different stages, among others Poul Alstrup, Ronald Belsey, Ruth Bjerregaard, John R. Bennett, Aase Christensen, J. Leigh Collis, Walford Gillison, Erna Hansen, Elis Hyldig, Inga Nielsen, Bodil Stephensen, Valborg Svendsen og Edith Veilbæk.

The staff of the photography department of the hospital gave me excellent assistance.

Mrs. Bente Vangedal translated the separate articles and Mrs. Bodil Svendsen, cand. mag., revised the English text of the review.

This study would, however, have come to nothing if it had not been for the extreme patience of all the persons who participated in the experiments and investigations.

I should like to extend my warmest thanks to all the persons mentioned and to the foundations which have supported my work.

Finally, I offer my sincere thanks to Karen, Lene og Dorte Boesby, who supported and assisted me in various ways during the preparation of this work.

This study was handed in to the Faculty of Medicine, Odense University for acceptance as a doctor's thesis on May 8th 1978.

Fruens Bøge, February 27th 1979

Steen Boesby

Denne afhandling er i forbindelse med omstående tidligere publicerede afhandlinger af det lægevidenskabelige fakultet ved Odense Universitet antaget til forsvar for den medicinske doktorgrad.

Odense, den 29. januar 1979

Jette Krarup
sekretær

PREVIOUS PUBLICATIONS

This review is based on the following papers, arranged in the order in which they were sent to Scand. J. Gastroent.

- I. Steen Boesby, Tommy Madsen & Hans Rahbek Sørensen: Gastro-Oesophageal Acid Reflux. Method for 12-Hour Continuous Recording of Oesophageal pH with Analysis of Records. Scand. J. Gastroent. 1975, 10: 379 - 384.
- II. Steen Boesby: Gastro-Oesophageal Acid Reflux and Sphincter Pressure in Normal Human Subjects. Scand. J. Gastroent. 1975, 10: 731 - 736.
- III. Steen Boesby: Effect of Changes in the Intra-gastric Milieu on Competence of the Gastro-Oesophageal Region. A Study in Normal Subjects. Scand. J. Gastroent. 1977, 12: 215 - 220.
- IV. Steen Boesby: Gastric Acid Secretion in Patients with Symptomatic Hiatus Hernia and Effect of a Modified Belsey MK IV Repair on Gastric Acid Secretion. Scand. J. Gastroent. 1977, 12: 401 - 406.
- V. Steen Boesby: Gastro-Oesophageal Sphincter Pressure, Motility and Acid Clearing. A Study of Hiatus Hernia Patients and Normal Subjects, and of the Effect of a Modified Belsey MK IV Repair on the Results of the Manometric and Acid Clearing Tests. Scand. J. Gastroent. 1977, 12: 407 - 416.
- VI. Steen Boesby: Gastro-Oesophageal Acid Reflux in Patients with Symptomatic Hiatus Hernia and Effect of a Modified Belsey MK IV Repair on Acid Reflux. Scand. J. Gastroent. 1977, 12: 553 - 569.

- VII. Steen Boesby: Relationship between Gastro-Oesophageal Acid Reflux, Basal Gastro-Oesophageal Sphincter Pressure and Gastric Acid Secretion.. Scand. J. Gastroent. 1977, 12: 547 - 551.
- VIII. Steen Boesby: The Acid Perfusion Test. A Study in Patients with Symptomatic Hiatus Hernia and of the Effect of a Modified Belsey MK IV Repair on the Test. Scand. J. Gastroent. 1977, 12: 241 - 244.
- IX. Steen Boesby: Continuous Oesophageal pH Recording and Acid Clearing Test. A Study of Reproducibility. Scand. J. Gastroent. 1977, 12: 245 - 247.

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CHAPTER 1 INTRODUCTION

1.0 Introduction

During the last decades steadily increasing interest in gastro-oesophageal reflux and reflux induced changes in the oesophagus has led to the development of several different methods of investigating the oesophagus and especially the physiological and pathophysiological conditions in the gastro-oesophageal region.

The aim of the present review is to describe some of these methods of investigation, to describe the results of the investigations in normal individuals and patients with hiatus hernia, to elucidate some physiological aspects of gastro-oesophageal reflux, to describe the relationships between the different methods of investigation and finally to point out possible uses of these methods in future research work.

The review is based on nine previously published papers, referred to in the text with roman numerals.

1.1 The gastro-oesophageal barrier

The gastro-oesophageal barrier is defined as the structures which contribute to the prevention of gastro-oesophageal reflux. Gastro-oesophageal reflux is the retrograde movement of gastric content into the oesophagus. The essential component in the barrier is the gastro-oesophageal sphincter (Cohen & Harris, 1970). The gastro-oesophageal region is influenced by hormonal, neurogenic, mechanical and pharmacological factors (Castell, 1975; Harvey, 1975; Christensen, 1976; Fisher & Cohen, 1976; Jennewein & Waldeck, 1976).

1.2 "Reflux model"

Gastro-oesophageal reflux is seen when intragastric pressure exceeds the resistance of the gastro-oesophageal barrier. As gastro-oesophageal reflux is seen in healthy,

asymptomatic individuals (Boesby, 1975 (II)), one would expect the development of symptomatic gastro-oesophageal reflux to be dependent on a) the duration of contact between the oesophageal mucosa and the reflux material, b) the composition of the reflux material and c) the sensitivity of the oesophageal mucosa to the reflux material. The duration of contact between the oesophageal mucosa and the reflux material (a) depends on the frequency with which reflux occurs, the volume of the reflux material and the ability of the oesophagus to return the reflux material.

1.3 Hiatus hernia

The diagnosis hiatus hernia is exclusively a radiological diagnosis.

In some previously published investigations, manometric characteristics were accepted as diagnostic of hiatus hernia (Code, Kelley, Schlegel & Olsen, 1962; Haddad, 1970; Butterfield, Struthers & Showalter, 1972; Habibulla, 1972). However, as the same kind of manometric characteristics are seen in normal subjects (Fox, Vidins & Beck, 1970; Kaye & Showalter, 1971), manometric characteristics cannot be regarded as evidence of hiatus hernia.

CHAPTER 2 METHODS

2.0 Introduction

The methods used to investigate the conditions of the gastro-oesophageal region and of the lower part of the oesophagus, were 12-hour continuous pH recordings five centimeters orally to the gastro-oesophageal sphincter, intraluminal oesophageal manometry, acid perfusion of the oesophagus, testing of the acid clearing ability of the oesophagus (the acid-clearing test) and measurements of gastric acid secretion. The manometric method is presented first, as manometric characteristics are used in several of the other methods of investigation.

2.1 Intraluminal oesophageal manometry

Continuously perfused open-tip catheters connected to external pressure transducers have been used in investigations of the pressure conditions in the upper part of the stomach, the gastro-oesophageal region and the oesophageal body since the late sixties. The application and development of the method have mainly been based on the results of in vitro investigations made by Pope (1967; 1970) and Waldeck, Jennewein, Siewert & Nieder (1973) and on the results of in vivo investigations carried out by Winans & Harris (1967), Pope (1970) and Cohen & Harris (1970). Dodds, Stef & Hogan (1976) have reviewed the factors that determine the accuracy and the possibilities for comparison of the results obtained by intraluminal oesophageal manometry.

The apparatus and the method used in the present series of investigations have been described (Boesby, 1975 (II) ; Boesby, Brandsborg, Brandsborg, Larsen & Pedersen, 1976). The technical characteristics of the apparatus are shown in Table I-2.

The calculations of the natural frequency (f_0) of the system and the degree of damping (α) were carried out in accordance with the formulae given by Warburg (1950). Further information about the pressure set-up is shown in Table II-2. Based on the characteristics mentioned, it can be concluded that the apparatus allows registration of low frequency pressures and that the volume displacement of the transducer is minimal compared with the compliance of the total system.

The technical characteristics of the pressure recording system are not the only points of importance in the evaluation of the results of oesophageal pressure measurements. The diameter of the pressure probe (Biancani, Spiro & Bejar, 1973; Biancani, Zabinski, Bejar & Spiro, 1973; Kaye & Showalter, 1974a; Lydon, Dodds, Hogan & Arndorfer,

1975) and the radial orientation of the catheter openings (Kaye & Showalter, 1971; Winans, 1972; 1977; Dodds, Miller, Hogan, Arndorfer, Lydon & Stef, 1975), are of importance for the results of the investigation. By using a probe provided with three holes at the same level and with diameters equal to the inner diameter of the catheter, the influence of the radial orientation of the side-holes should be eliminated, as a rise of pressure in the system demands occlusion of all three holes at the same time. A probe with an outer diameter of 2.5 mm for measuring the pressure in the gastro-oesophageal sphincter is suggested as best suited for measuring pressures that differentiate clinically competent and incompetent sphincters (Biancani, Spiro & Bejar, 1973; Wienbeck, 1976).

The withdrawal of the probe through the gastro-oesophageal sphincter during the measurement of sphincter pressure can be done in three different ways; intermittent withdrawal without swallowing, intermittent withdrawal with swallowing at each level and continuous withdrawal (Pedersen & Boesby, 1976). Intermittent withdrawal of the probe with swallowing at each level can be carried out in a variety of patient material, as the method neither demands omission of swallowing nor prolonged cessation of respiration in the expiratory phase. This was the method used in the series of investigations presented in this study.

Movements of the sphincter region during swallowing and during respiration may interfere with the investigation and induce artefacts (Dodds, Stewart, Hogan, Stef & Arndorfer, 1974). This seems to be of minor practical importance in the applied method, as the results of sphincter pressure measurements have proved to be reproducible (Pedersen, 1975a).

A consequence of the technical characteristics of the equipment together with the flow used is that the system does not allow registration of rapidly changing major pres-

Table I-2: Technical characteristics of the pressure recording system.

1. Compliance	1.3	$\mu\text{l/mmHg}$
2. Volume displacement (Elema-Schönander EMT 35)	9×10^{-4}	$\mu\text{l/mmHg}$
3. f_0 (natural frequency)	1.6	Hz
4. α (degree of damping)	2.0	

Table II-2: Specifications of the pressure recording system.

1. Length of pressure probe	90	cm
2. Pressure catheter diameter	i.d.	1.4 mm
(Clay Adams PE 160)	o.d.	1.6 mm
3. Metal capsule with three side-holes at the same level.		
Diameter of capsule	2.5	mm
Length of capsule	1.5	cm
Diameter of side-holes	1.4	mm
4. Flow from infusion pump		
(B. Braun Melsungen, Unita I)	0.5	ml/min.

sure waves, as seen during the propagation of the peristaltic pressure wave, for which reason measurements of peristaltic pressure amplitude were not included in this study.

Measurements of the amplitude of peristaltic pressure demand measuring systems with minimal compliance (Arndorfer, Stef, Dodds, Linehan & Hogan, 1977) or systems connected to high perfusion flow (Waldeck, Jennewein, Siewert & Nieder, 1973). Intraluminal tip-transducers are also suitable (Wallin, Boesby & Madsen, 1978).

All measurements of sphincter pressure were carried out with the subject having fasted for at least five hours. The factors mentioned (1.1) which influence sphincter pressure should hereby be reduced to a minimum.

The pressure transducers were positioned ten centimeters above the couch, and the patient was placed in a supine position during the examination, the influence of hydrostatic factors thus being eliminated.

Gastro-oesophageal sphincter pressure is defined as maximum sphincter pressure during expiration less the expiratory pressure in the gastric fundus. It is thus the measurement of a pressure gradient and not that of an absolute pressure.

The reading of the pressure curves can be done in various ways; inspiratory pressure, mean pressure as well as expiratory pressure can be used (Dodds, Stef & Hogan, 1976) and each method of reading the curves will lead to different results.

All results in the present study were obtained by using the apparatus and the method described. The conditions under which the examinations were carried out remained unchanged. The method allows registration of intragastric pressure, intrasphincteric pressure, decline in intrasphincteric pressure during swallowing, basal pressure in the oesophageal body and the propagation of the peristaltic pressure wave in the oesophageal body (normally propagat-

ing, retrograde, simultaneous). The method does not allow registration of the duration of sphincter relaxation or the amplitude of the peristaltic contractions.

2.2 Acid perfusion in the oesophagus

The need for a reliable method of objective differentiation between symptoms arising in the oesophagus and symptoms of the same nature and with the same localisation, but with another origin, led to the development of the acid perfusion test by Bernstein & Baker (1958).

Balloon distension of the oesophagus and short-term instillation of test solutions into the oesophagus in an attempt to explain symptoms of oesophageal origin and to develop such a test, did not lead to the development of a clinically useful test (Moersch & Miller, 1943; Baylis, Kauntze & Trounce, 1955).

As the symptom producing effect of a test solution not only depends on the sensitivity of the receptor organ and the concentration of the test compound, but also depends on the duration of contact between receptor organ and test solution as well as the total volume of the test solution, Bernstein & Baker (1958) chose to perfuse the oesophagus with isotonic saline or isotonic glucose alternating with 0.1 n HCl for up to 30 minutes with a flow of 6-7 ml per minute.

Originally the test was introduced to demonstrate evidence of oesophagitis. Later studies (Siegel & Hendrix, 1963; Skinner & Booth, 1970; Sladen, Riddell & Willoughby, 1975) could not confirm any close relationship between a positive test and oesophagitis, so the acid perfusion test must be regarded as a test for symptoms of oesophageal origin (Bennett & Atkinson, 1966).

Most descriptions of acid perfusion investigations are modifications of the original method (Tuttle, Bettarello & Grossman, 1960; Bernstein, Fruin & Pacini, 1962; Siegel &

Hendrix, 1963; Bennett & Atkinson, 1966; Haddad, 1970; Ismail-Beigi, Horton & Pope, 1970; Skinner & Booth, 1970; Garabedian, 1971; Benz, Hootkin, Margulies, Donner, Cauthorne & Hendrix, 1972; Behar, Biancani, Spiro & Storer, 1974; Sladen et al., 1975; Boesby, 1977 (VIII)).

In principle, the aim of the test is to provoke oesophageal symptoms; thus reproduction of the patient's spontaneous symptoms or parts thereof during acid perfusion is necessary for the result to be regarded as positive.

In VIII a method is described which, from a theoretical point of view, should be useful in daily clinical work, and which was used in the present study.

2.3 Continuous pH recording in the oesophagus

Application of a pH electrode in the oesophagus to demonstrate gastro-oesophageal acid reflux was first described by Tuttle & Grossman in 1958. Since then several short-term methods for the demonstration of acid reflux have been described (Tuttle, Bettarello & Grossman, 1960; Morgan, 1962; Morgan, Hill & Selby, 1963; Kantrowitz, Corson, Fleischli & Skinner, 1969; Lockwood & Borgeskov, 1969; Skinner & Booth, 1970; Benz, Hootkin, Margulies, Donner, Cauthorne & Hendrix, 1972).

Prolonged pH recording in the distal end of the oesophagus for studying gastro-oesophageal reflux was described by Spencer (1969) and recommended as a physiological method, the results of which could add new aspects to the understanding of reflux mechanisms and be used to evaluate the effect of anti-reflux treatment.

The method has since been used in several investigations. The duration of examination has varied (6 hours (Rendall, 1972), 12 hours (Boesby, Madsen & Sørensen, 1975 (I)), 13½ hours (Lichter, 1974), 15 hours (Woodward, 1970; Habibulla, Ammann & Collis, 1971; Stanciu & Bennett, 1972),

18 hours (Spencer, 1969) and 24 hours (Johnson & DeMeester, 1974a)).

Originally the pH electrode was positioned according to radiological criteria at a point between the middle and lower third of the oesophagus, whereas in later investigations the electrode was positioned and fixed five centimeters orally to the gastro-oesophageal sphincter, usually indicated by manometric characteristics.

As the factors which regulate the gastro-oesophageal barrier (1.1) may influence the results, a standardization of investigation conditions must be attempted (Boesby et al., 1975 (I)).

The results of a continuous pH recording can be stated in different ways, depending on the criteria used for reflux. The possible variables are the duration of pH below certain limits stated in minutes or as percentages of the total recording period, the number of reflux episodes, the mean duration of the reflux episodes and the duration of the individual episodes (Spencer, 1969; Woodward, 1970; Habibulla et al., 1971; Stanciu & Bennett, 1972; Lichter, 1974; Boesby et al., 1975 (I); Atkinson & van Gelder, 1977).

A reflux episode is defined as a sudden fall of at least 2 pH units to a level below 5, five centimeters orally to the gastro-oesophageal sphincter. A "score" including some of the variables mentioned was used by Johnson & DeMeester (1974a). In another case the area between the curve and a fixed baseline was measured by planimetry and used as a variable (Pattrick, 1970).

It is possible by direct reading of the curves to state the results of the investigation by the variables mentioned. However, the development of an automatic analyser (Boesby et al., 1975 (I); Madsen & Boesby, 1977) has simplified the reading of the curves. The accuracy of the analysis is good (coefficient of variation: 0.0001 - 0.10), and the reading excludes subjective factors. An automatic analysis accord-

ing to a single pre-set criterion has been described by Lichter (1974).

In an attempt to simplify the statement of the investigation results and to give the examination a practical clinical form, I have chosen to state the results as the duration of pH below 2.3, 3, 4, and 5 as percentages of the 12 hours the examination lasted, and the number of reflux episodes. This brings the investigation into line with the "reflux model" described (1.2).

Studies of the stability of the measuring system (Boesby et al., 1975 (I)) have shown that the total drift of the whole monitoring system is 0.0 - 0.2 pH units. The reproducibility of the method (Boesby, 1977 (IX)) was studied in repeated examinations of one normal subject. The coefficient of variation varied between 0.61 and 0.94. The investigation showed that in spite of considerable variation, the results of the pH measurements stayed within normal range.

2.4 The acid-clearing test

The ability of the oesophagus to dispose of reflux material is one of the functions determining the duration of contact between the oesophageal mucosa and the reflux material. Booth, Kemmerer & Skinner (1968) developed a method for evaluating this function: the acid-clearing test.

As a measurement of the function they used the number of swallows needed to raise pH above 6 five centimeters orally to the gastro-oesophageal sphincter after instillation of 15 ml 0.1 n HCl fifteen centimeters orally to the sphincter. In later investigations by the same team (Skinner & Booth, 1970) the limit was put at pH above 5. The size of the bolus as well as the position of the bolus and the position of the pH electrode were the same in later studies (Stanciu & Bennett, 1974a; Krejs, Seefeld, Brändli, Bron, Caro, Schmid & Blum, 1976; Boesby, 1977 (V)).

The frequency of swallowing does not seem to influence the results (Booth et al., 1968). Krejs et al. (1976) let the patients swallow when they wanted to, while Booth et al. (1968) and Stanciu & Bennett (1974a) chose to ask the patients to swallow every 30 seconds.

The position of the patient during the examination is of great importance, as elevation of the upper part of the body increases the acid-clearing ability (Stanciu & Bennett, 1974a).

In some cases spontaneous reflux occurs during the examination. This means that neutral pH must be reobtained before the examination can start again, or that the examination must be carried out at another time. In a few cases the examination must be abandoned. Some patients have an almost permanently incompetent reflux barrier, and it is not possible to carry out the examination, as pH must be assumed to be above 5 before the examination starts. Some patients have such a poor clearing ability that a pH above 5 is not reached even after 30 swallows. The examination is terminated at the 31st swallow, as a continuation tires the patient and would hardly give further information.

In the present study (Boesby, 1977 (V)) the method chosen was the one described by Skinner & Booth (1970). The reproducibility of the results with this method is good (coefficient of variation: 0.22) (Boesby, 1977 (IX)).

2.5 Gastric acid secretion

Measurement of gastric acid secretion gives a partial picture of the composition of the material available for reflux, and such measurements were therefore included in the research programme.

Fasting acid secretion, basal acid secretion and gastric secretion during pentagastrin stimulation are all included as variables in the investigation as described in IV. The investigation was carried out as routine tests at the

Department of Medical Gastroenterology S, Odense University Hospital.

CHAPTER 3 MATERIALS

3.0 Normomaterial

The normomaterial is described in the separate papers (II, III, IV, V, VI and IX). It was composed of 37 healthy subjects in the manometric study and of 26 healthy subjects in the continuous pH monitoring and acid-clearing studies.

3.1 Patient material

The patient material is described in the separate papers (IV, V, VI, VII, VIII). The material was selected from a group of patients referred to the Oesophagus Laboratory, the Department of Thoracic and Cardiovascular Surgery T, Odense University Hospital for further elucidation of symptoms which might be ascribed to the oesophagus or to a disease demonstrated in the oesophagus.

The composition of the material and the selection of patients are described in the separate papers. All patients referred to the laboratory during the period of investigation who fulfilled the criteria for inclusion in the different material groups and who underwent at least one of the examinations, were included in the study.

3.2 Percentage of completed investigations

During the period from May 1st 1973 to November 1st 1976 615 manometric investigations were carried out in 290 individuals. In 11 individuals the investigations could not be completed due to narrowing of the nose (7 individuals) or to stricture of the oesophagus (4 individuals). The percentage of successful manometric investigations was thus 96.

Continuous pH recording in the oesophagus was attempted in 153 individuals. 146 completed the investigations, the number of registrations adding up to 220. The percentage

of successful recordings was thus 95. The 7 who failed to complete the recording had narrowing of the nose.

The acid-clearing test was attempted in all cases where the pH probe could be positioned. In four cases the investigation could not be performed owing to massive reflux, and in one case it was not possible to obtain the necessary cooperation of the patient. Thus the investigation was carried out in 92% of the cases.

The acid perfusion test can be accomplished in all cases where manometry is carried out; however, it was only carried out in patients where symptomatology made the investigation relevant.

Gastric acid secretion was measured in all patients who fulfilled the criterion of inclusion: "radiologically verified sliding hiatus hernia".

3.3 Definition of symptoms

The symptoms which are registered in the separate papers (IV, V, VI and VIII) and which are considered to be the most important symptoms of gastro-oesophageal reflux, are heartburn, pain, dysphagia.

Heartburn is defined as a burning, painful sensation in the upper part of the epigastrium or behind the lower part of the sternum, provoked or accentuated by stooping, lifting or a horizontal position.

Pain is defined as pain localized to the upper epigastrium behind the lower part of the sternum, possibly with radiation to the neck.

Dysphagia is defined as a subjective sensation, downwards behind the sternum, of difficulty in swallowing.

Other symptoms have been associated with the combination of hiatus hernia and gastro-oesophageal reflux, and Brennan, Trindade, Rozycki & Giles (1974) have set up a differentiated grading system for symptoms of reflux. However, these other symptoms are rarely seen without the

presence of one of the above-mentioned symptoms.

CHAPTER 4 RESULTS IN NORMAL SUBJECTS. AND CONTROLS

4.0 Introduction

The control material which has been described and which forms the basis for evaluating the results of investigations in patients, mainly consisted of patients who did not have symptoms ascribable to the oesophagus, but who were in hospital for some other reason. Material of this composition is called control material or controls, while material composed of healthy individuals without symptoms, recruited among students, hospital staff and their friends is called normomaterial.

4.1 The gastro-oesophageal sphincter pressure

The results of measurements of gastro-oesophageal sphincter pressure not only depend on the conditions under which the measurements are carried out, but also on the technical equipment and the method (2.1). The results from different centres thus show great variation (Pedersen, 1975b; Waldeck & Jennewein, 1976). Important information about the apparatus and the methods used is often missing, which means that direct comparison of the results is impossible. If all the information is not accessible, the "oesophageal pressure values are as ambiguous as a gas pressure measured at an unspecified gas temperature and volume" (Dodds, Stef & Hogan, 1976). This stresses the necessity for all laboratories dealing with pressure measurements in the oesophagus to state the technical characteristics of the apparatus, the method of examination and the reading of the curves and to state the normal range of the specific laboratory.

In this study the normal range of the gastro-oesophageal sphincter pressure is 8-24 mmHg (Boesby, 1977 (V)).

4.2 Acid perfusion of the oesophagus

The performance of the acid perfusion test in healthy, asymptomatic individuals in an attempt to achieve a normo-material is, so to say, meaningless, since a positive test implies reproduction of spontaneous symptoms.

Investigations of oesophageal acid sensitivity in asymptomatic subjects have, however, shown that acid perfusion evokes pain in 5% (Bernstein & Baker, 1958) to 50% (Bennett & Atkinson, 1966) of the subjects involved.

4.3 Continuous pH recording in the oesophagus

The results of continuous pH recording in the oesophagus in normal subjects or controls are stated in Table I-4.

Direct comparison of the results of the different investigations was not possible, as both investigation conditions and the composition of material were different.

Spencer's (1969) control material consisted of one normal subject, 6 patients with duodenal ulcer, 3 patients with x-ray negative dyspepsia and one patient with gallstones. None of the controls presented symptoms or radiological signs of hiatus hernia. Johnson & DeMeester (1974a) presented a control material consisting of patients hospitalized for operation of inguinal hernia or some other "nongastroenterologic illness".

Normomaterials have been described by Habibulla, Ammann & Collis (1971), Rendall (1972), Boesby (1975 (II)), Irvin & Perez-Avila (1977). Stanciu, Hoare & Bennett (1977) selected 29 persons from a group of 42, of whom 26 were normal subjects and 16 had "irritant bowel syndrome".

Distribution on age groups in materials has only been stated by Stanciu et al. (1977) and in II. This seems of minor practical importance, since it has not been possible to show relationships between age and the results of the investigation (Boesby, 1977 (VI)).

In most studies the individual was not restricted to a fixed position during monitoring, and intake of food with a pH above 5 was allowed. On the other hand smoking was prohibited, as smoking reduces the competence of the gastro-oesophageal region (Stanciu & Bennett, 1972). Sleeping medicine was used in a few investigations. Studies of the effect on acid reflux tendency of the sleeping medicine administered have not been published.

Stanciu et al. (1977) and Irvin & Perez-Avila (1977) described a method and investigation conditions comparable to those of the present study (Boesby et al., 1975 (I); Boesby, 1975 (II)) and consequently the results are in agreement.

As a whole, the results of the investigations mentioned show that reflux of acid secretions into the oesophagus in asymptomatic individuals is an expression of a physiological incompetence of the gastro-oesophageal barrier.

4.4 The acid-clearing test

The results of the acid-clearing test in normal subjects and controls are stated in Table II-4.

As previously pointed out (2.4), the procedures used in the published studies are almost identical with the original method. The results of the studies are very similar in the cases where the limit of pH above 5 was used.

Booth, Kemmerer & Skinner (1968), Skinner & Booth (1970) and Stanciu & Bennett (1973a) examined controls, while Krejs, Seefeld, Brändli, Bron, Caro, Schmid & Blum (1976) and Boesby (1977 (V)) examined normal subjects.

The results show that normal individuals use 4 to 16 swallows to clear an acid bolus of 15 ml 0.1 n HCl from the distal part of the oesophagus.

4.5 Gastric acid secretion

The present study did not include comparisons between acid secretion in normal subjects and patients, so the vari-

Table I-4: The results of continuous pH recording in normal subjects and controls. In all cases the mean value is stated. Figures in brackets have been subjected to calculations (the results originally stated in minutes). N is the number of subjects included in the investigations. D is the duration of the investigation in hours. Underlined figures state one standard deviation (SD). \$ states mean value -SD to mean value +SD. \$\$ marks that the figures have been read from a diagram. ' states the 5% - 95% percentiles.

Author	N	D	Duration of pH < the limits stated				Number of reflux episodes
			2.3 %	3 %	4 %	5 %	
Spencer (1969)	11	18	-	-	(3.8) (2.2-5.3) \$	-	-
Habibulla et al. (1971)	5	10	-	-	0	0	0
Rendall (1972)	11	6	-	-	2.4 \$\$	-	-
Johnson & DeMeester (1974a)	15	24	-	-	1.5 <u>1.4</u>	-	20.6 <u>14.8</u>
Boesby (1975(II))	26	12	0.08 0-0.76'	0.18 0-1.43'	0.46 0-2.78'	1.02 0-6.59'	5 0-31'
Stanciu et al. (1977)	29	15	-	0.07 <u>0.09</u>	0.17 <u>0.23</u>	0.26 <u>0.41</u>	2.72 <u>2.45</u>
Irvin & Perez-Avila (1977)	10	15	-	-	(0.5) (0.4-0.7) \$	(1.2) (0.8-1.5) \$	-

ables of gastric acid secretion were not measured in normal subjects.

4.6 Intragastric milieu and the gastro-oesophageal barrier
Of the hitherto reported studies of continuous pH recording in the oesophagus only a few mention the composition of the potential reflux material (Spencer, 1969; Lichter, 1974; Stanciu, 1975). Several investigations have shown that pressure in the gastro-oesophageal region is modified under the influence of factors which also modify the acid content of the stomach (Castell & Harris, 1970; Castell, 1971; Hollis, Levine & Castell, 1972). Only one investigation has been published on the effect of changes in the intragastric milieu on competence of the gastro-oesophageal region measured directly by intra-oesophageal pH (Boesby, 1977 (III)).

In the present study changes of the intragastric milieu were induced in ten normal subjects by continuous infusion of pentagastrin, by intravenous bolus injection of insulin or by direct instillation of hydrochloric acid into the stomach.

Intra-oesophageal pH was measured under basal conditions and during reflux provocation (leg raising) before and after induced changes in the intragastric milieu. Intragastric pH was measured, and in all cases a decrease was seen. The investigation showed that intragastric instillation of hydrochloric acid was followed by an increased tendency to reflux, whereas this was not the case during pentagastrin infusion and after insulin injection.

Intragastric instillation of hydrochloric acid is followed by a reduction of sphincter pressure (Castell & Harris, 1970). The results in III are in agreement with this observation and the interpretation of the gastro-oesophageal barrier (1.1). The mechanism behind this incompetence of the gastro-oesophageal region has not been fully elucidated, however. It was attempted to explain changes in

Table II-4: Results of the acid-clearing test in normal subjects and controls. N is the number of individuals involved.

Author	N	pH limit	Number of swallows
Booth et al. (1968)	21	≥ 6	4 - 10 (range)
Skinner & Booth (1970)	28	≥ 5	≤ 10
Stanciu & Bennett (1973a)	14	≥ 5	4 - 12 (range)
Krejs et al. (1976)	24	≥ 6	≤ 32
Boesby (1977 (V))	26	≥ 5	4 - 16 (range)

sphincter pressure by changes in serum gastrin (Castell & Harris, 1970); but later investigations were not able to confirm such a simple relationship (Sturdevant, 1974).

Animal experiments have shown that intragastric instillation of isotonic saline is first followed by a pressure rise in the gastro-oesophageal region and then, with an increase of volume, by a pressure fall (Titchen & Wheeler, 1971). This is explained as a vago-vagally mediated reflex. Thus it is possible that an increase of intragastric volume produces a fall of the pressure in the gastro-oesophageal region, reducing the resistance against reflux.

Continuous infusion of pentagastrin in the same dosage as that used in III does not lead to significant changes in sphincter pressure (Frank, Walker & Fordtran, 1973), but produces maximal stimulation of gastric acid secretion (Brooks, Johnson & Grossman, 1970). The results of the short-term pH investigation in III showed that the competence of the gastro-oesophageal region was unaltered during pentagastrin stimulation of gastric acid secretion. In agreement with this observation, in most papers no correlation is seen between maximal gastric acid secretion and the results of continuous pH recording in the oesophagus (Stanciu, 1975; Boesby, 1977 (VII)) (6.2).

Bolus injection of insulin in the same dosage as that used in III, was followed by a decrease of pressure in the gastro-oesophageal region parallel to an increase of intragastric acidity (Castell, 1971). The investigation showed that the competence of the region was unaltered. This may be due to an insufficient decrease in pressure or to a change in the reaction of the region to reflux provocation during insulin hypoglycaemia.

The pressure response of the gastro-oesophageal region to reflux provocation during pentagastrin infusion, during insulin induced hypoglycaemia and after intragastric instillation of hydrochloric acid has still not been subjected to

research.

CHAPTER 5 RESULTS IN PATIENTS

5.0 Introduction

The results of patient studies are presented in the same order as that of the individual methods described.

5.1 Manometric investigations

The introduction of perfused catheter systems connected to external pressure transducers for measuring gastro-oesophageal sphincter pressure meant that a reliable method for pressure measurements was available. Interest was concentrated on the relationship between sphincter pressure and symptomatology and mainly on the relationship between low sphincter pressure and symptoms of gastro-oesophageal reflux.

Winans & Harris (1967) found that measurement of basal gastro-oesophageal sphincter pressure permitted a clear differentiation between normal subjects and patients with radiologically verified gastro-oesophageal reflux. Cohen & Harris (1971) demonstrated that patients with massive symptoms of gastro-oesophageal reflux, with or without radiologically verified hiatus hernia, had a lower basal sphincter pressure than asymptomatic individuals, whether they had hiatus hernia or not, and there was no overlap between the two groups. These results indicate that low basal pressure predisposes to reflux, whereas a hiatus hernia per se is not of any importance. Such a total differentiation between patients with symptoms on one hand, and asymptomatic individuals on the other on the basis of basal sphincter pressure measurements has not been confirmed in the many other studies published (Pope, 1967; Haddad, 1970; Skinner & Booth, 1970; Csendes & Larrain, 1972; Behar, Biancani, Spiro & Storer, 1974; Henderson, Mugashe, Jeejeebhoy, Cullen, Boszko, Szczepanski & Marry-

att, 1974; Siewert, Weiser, Jennewein & Waldeck, 1974; Biancani, Zabinski & Behar, 1975; Ellis, El-Kurd & Gibb, 1976; Krejs, Seefeld, Brändli, Bron, Caro, Schmid & Blum, 1976; Boesby, 1977 (V); Stanciu, Hoare & Bennett, 1977). Differences in the composition of patient material and in the apparatus and methods used probably account for this. In all investigations a lower mean basal sphincter pressure was seen in patients with symptoms than in asymptomatic individuals.

The degree of severity of the symptoms does not seem to be related to the basal sphincter pressure (Boesby, 1977 (V)). In a group of patients with peptic stricture of the oesophagus sphincter pressure was shown to overlap that of normal subjects (Larrain, Csendes, Uribe & Ayala, 1973).

Heitmann (1969) made a subgrouping of patients with radiologically verified hiatus hernia based on symptomatology and found that low pressure was related to the symptom of heartburn, and high pressure was related to the symptoms of dysphagia and retrosternal pain, whereas normal pressure only in a few cases was associated with symptoms that could be ascribed to the oesophagus. These results were in part confirmed by Pedersen (1975c).

In V there were no patients with sphincter pressure above the normal upper limit. The reason for this may be that most of the patients examined had symptoms of gastro-oesophageal reflux. It must also be stated that the pressure probe used for the examinations registered the lowest pressure of the region.

As determination of the basal gastro-oesophageal sphincter pressure only gives an instantaneous picture of the competence of the gastro-oesophageal barrier, stimulation of the region has been attempted in order to get a better impression of the function.

Lind, Warrian & Wanklin (1966) showed that the cli-

nically competent sphincter region responded actively to raised intragastric pressure with a rise in sphincter pressure exceeding that of the rise in intragastric pressure. This observation was confirmed in several later investigations (Cohen & Harris, 1971; Lipshutz, Eckert, Gaskins, Blanton & Lukash, 1974; Siewert et al., 1974; Ellis et al., 1976). In these investigations it was also shown that the clinically incompetent gastro-oesophageal barrier responded with a pressure change which was less or equal to the intragastric pressure change. Dodds, Hogan, Miller, Stef, Arndorfer & Lydon (1975) could not confirm that the sphincter region responded actively to an intragastric rise in pressure.

Stimulation of the region by pentagastrin demonstrated that in patients with symptoms attributable to reflux there was a reduced response to pentagastrin compared with normal individuals (Lipshutz et al., 1974). This observation has been used for further subgrouping of patients with hiatus hernia (Siewert et al., 1974).

Biancani, Zabinski & Behar (1975) studied the mechanical characteristics of the gastro-oesophageal region and found that the pressure-diameter curves for competent and incompetent sphincters were different. Incompetent sphincters had lower pressures with all probe diameters and the pressure increased with an increase of the probe diameter. Competent sphincters showed high pressures with small pressure probe diameters, and following an increase of the probe diameter the pressure was first seen to fall and then to rise again.

To what extent the differences mentioned, the low sphincter pressure and the other characteristics of the sphincter region in patients with symptoms of gastro-oesophageal reflux, can be explained by reduction or absence of neurogenic or hormonal stimulation or inhibition by neurogenic or hormonal mechanisms still needs to be clarified.

Disorders of sphincter relaxation and of oesophageal motility were only demonstrated in a few cases in the present study and in only a few of these cases could the disorders be traced to the actual symptomatology of the patients (Boesby, 1977 (V)). Siegel & Hendrix (1963) demonstrated disorders of the motility of the oesophageal body in patients where acid perfusion of the oesophagus provoked the symptom of heartburn. In cases where dysphagia was a prominent symptom, Cross & Jones (1973) often demonstrated motility changes in the oesophageal body. In animal experiments Henderson et al. (1974) were able to provoke motility disturbances in the oesophageal body and in the gastro-oesophageal sphincter by inducing oesophagitic changes. The motility disturbances were of the same kind as those found in patients with symptoms of reflux and oesophagitis. In the experimental study the disorders proved to be reversible.

The aim of surgical treatment of gastro-oesophageal reflux is to recreate the competence of the gastro-oesophageal region and thus prevent reflux. Consequently, the purpose of the more recent surgical procedures is to re-establish the anatomical conditions in the gastro-oesophageal region and to recreate a barrier against gastro-oesophageal reflux (Nissen, 1961; Hill, 1967; Skinner & Belsey, 1967; Collis, 1968). In accordance with this purpose all published studies demonstrate an increase of the basal gastro-oesophageal sphincter pressure after operation a.m. Nissen (Battle, Nyhus & Bombeck, 1973; Biancani et al., 1975; Bowes & Sarna, 1975; DeMeester & Johnson, 1975; Bushkin, Neustein, Parker & Woodward, 1977), a.m. Hill (Csendes & Larrain, 1972; Behar, Sheahan, Biancani, Spiro & Storer, 1975; DiMarino, Rosato, Rosato & Cohen, 1975), a.m. Belsey MK IV (Lipshutz et al., 1974; Behar et al., 1975) and other surgical procedures (Ellis et al., 1976; Boesby, 1977 (V)). However, postoperative, normal, basal

sphincter pressure is not a prerequisite for being asymptomatic. In postoperatively asymptomatic individuals low sphincter pressures (Bombeck, Battle & Nyhus, 1973; Bowes & Sarna, 1975; DiMarino et al., 1975; Boesby, 1977 (v)) as well as high sphincter pressures (DeMeester & Johnson, 1975) have been measured.

Investigations of the reaction of the sphincter region to an intragastric rise in pressure after reflux-preventive surgery have not led to unambiguous results. The sphincter region often reacts subnormally (Behar et al., 1975; Bowes & Sarna, 1975; DiMarino et al., 1975). Ellis et al., (1976), however, were not able to demonstrate any difference between patients and normal subjects. Lipshutz et al. (1974) also demonstrated that the sphincter region responded normally to an intragastric rise in pressure, and further, they were able to demonstrate that the region responded normally to stimulation with pentagastrin.

The mechanical characteristics of the sphincter are normalized after operation a.m. Nissen (Biancani et al., 1975).

It is not possible to give an immediate explanation of the changes which have been demonstrated regarding sphincter pressure and sphincter function after the various surgical procedures. The changes may be due to simple mechanical conditions, to an alteration of the muscles in the sphincter region or to incorporation of part of the fundic muscle with specialized motor function.

The information available for evaluating the influence of mechanical conditions on the increase of sphincter pressure after reflux-preventive surgery, is based on animal experiments. Siewert, Jennewein, Waldeck & Peiper (1973) demonstrated that surgical removal of the muscles in the sphincter region (myomectomy) led to a decrease of pressure in the gastro-oesophageal region; subsequent fundoplication was followed by a rise of pressure in the region to

values similar to those of normal, basal sphincter pressure. Condon, Kraus & Wollheim (1976) were able to confirm these results and further demonstrated that fundoplication was followed by a normal response of the gastro-oesophageal region to intragastric rise in pressure. There was a direct proportional relationship between intragastric rise in pressure and increase of pressure in the gastro-oesophageal region. They concluded that the effect was solely mechanical and without relation to the sphincter.

Animal experiments and in vitro investigations have demonstrated that the anterior part of the gastric fundus responds to pentagastrin in the same way as the gastro-oesophageal region (Siewert et al., 1973). Human investigations in this field have not been carried out. If human investigations revealed similar conditions, it would be possible to explain the results of the investigations which have demonstrated that the sphincter region responds normally to pentagastrin stimulation after reflux-preventive surgery (Lipshutz et al., 1974). If it were possible to identify the area peroperatively, it would also be possible to incorporate the area into the plication, in which case the probable result would be a normally responding gastro-oesophageal region.

The increase of sphincter pressure after reflux-preventive surgery is hardly caused by healing of the reflux-induced changes at the distal end of the oesophagus, as intensive medical treatment of gastro-oesophageal reflux and succeeding lack of symptoms is not followed by an increase of sphincter pressure (Battle et al., 1973; Behar et al., 1974). However, one experimental investigation in cats has demonstrated that oesophagitis is followed by a decrease of sphincter pressure and healing by an increase of pressure to normal (Eastwood, Castell & Higgs, 1975).

5.2 Acid perfusion of the oesophagus

The evaluation and description of results published regard-

ing the acid perfusion test, are restricted by the fact that the investigations were carried out on very inhomogeneous and varied patient material, that different methods were used (2.2), that different definitions of positive and negative results were applied and that symptoms were variously defined.

In the investigations in which special interest was concentrated on the result of the test in patients with symptoms of gastro-oesophageal reflux, the incidence of positive test results is given as 100% (Benz, Hootkin, Margulies, Donner, Cauthorne & Hendrix, 1972; Behar, Biancani, Spiro & Storer, 1974), 82% (Miller, Hogan, Dodds, Arndorfer & Stef, 1974), 79% (Tuttle, Bettarello & Grossman, 1960), 76% (Bennett & Atkinson, 1966), 73% (Sladen, Riddell & Willoughby, 1975), 72% (Skinner & Booth, 1970), 54% (Krejs, Seefeld, Brändli, Bron, Caro, Schmid & Blum, 1976) and 44% (Boesby, 1977 (VIII)).

In cases where the test proved positive in 100% of the patients, it was used in the selection of patients, a positive test being the criterion of inclusion in the other examinations.

Spencer (1972) examined patients with various upper abdominal diseases and found the test positive in 29% to 67% of the patients examined. The actual symptomatology was not stated.

The mechanism behind the provocation of symptoms during acid perfusion of the oesophagus has been discussed and does not seem to be clarified. Siegel & Hendrix (1963) demonstrated that acid perfusion provoked spasm-like motility changes in the oesophageal body parallel to the provocation of symptoms, and therefore considered the spasms to be the cause of the symptoms. In Bernstein & Baker's (1958) original work no spasms were seen in the oesophagus during acid perfusion, and the symptoms were thought to be caused by direct contact between the sensory nerve endings and the acid, an interpretation shared by Tuttle,

Rufin & Bettarello (1961). Animal experiments and human investigations have rendered it probable that the hydrogen ion penetrates the oesophageal mucosa, making contact between the sensory nerve endings and the hydrogen ion possible (Safaie-Shirazi, DenBesten & Zike, 1975; Safaie-Shirazi, 1977). Distension of the oesophagus may provoke pain and heartburn-like symptoms (Baylis, Kauntze & Trounce, 1955). This cannot, however, be the ordinary mechanism, as saline perfusion is usually completed without provoking symptoms.

It is possible that the symptoms may be provoked from receptors in the stomach, as the acid passes from the oesophagus into the stomach during perfusion (Moraes-Filho & Bettarello, 1974). In an attempt to avoid false positive results of the test, some investigators have alternated between acid perfusion of the oesophagus and of the stomach (Bernstein & Baker, 1958; Tuttle et al., 1960). In VIII simultaneous instillation of equimolar amounts of alkali into the stomach were used to neutralize the acid.

Several investigations have demonstrated that following intensive antacid treatment of patients with positive acid perfusion tests, the tests become negative, although gastro-oesophageal reflux can still be demonstrated (Tuttle et al., 1960; Benz et al., 1972). The reason for this could be that the barrier of the oesophageal mucosa against the hydrogen ion is reestablished during the treatment.

It must be pointed out that a prerequisite for the establishment of a correlation between symptoms and a positive test is that the patients have not been free of symptoms for some time prior to the test.

The purpose of the acid perfusion test is to provoke such symptoms as can be ascribed to the oesophagus and which are associated with gastro-oesophageal reflux. In VIII the test was positive in only 44% of the patients. This percentage is low compared with most other published results and may be due to differences in method and se-

lection of patients.

The reflux material contains not only hydrochloric acid; pepsin, bile (Stol, Murphy & Collis, 1974) and proteolytic pancreatic enzyme (Wickbom, Bushkin & Woodward, 1974) may also be components of the reflux material. Heartburn is seen in patients with achlorhydria and in patients who have undergone total gastrectomy (Wickbom et al., 1974).

It is still not clarified whether the acid per se provokes the spontaneous symptoms in the patients. It is probable that for the acid to provoke symptoms the mucosal barrier must be under the influence of pepsin and /or bile (Safaie-Shirazi et al., 1975; Safaie-Shirazi, 1977). Some patients have symptoms which cannot be provoked by acid, but which are reproduced by perfusion with 0.1 n NaOH (Vela & Akdamar, 1975).

Oesophageal perfusion tests with different test solutions, e.g. containing bile salts (Orlando & Bozyski, 1973), may contribute to the understanding of the provocation of symptoms ascribable to the oesophagus and further lead to the development of a clinically useful test.

It can be concluded that the test in its present set-up can be used for determining whether the patient's spontaneous symptoms may be of oesophageal origin; a negative test does not allow any conclusion regarding the genesis of the symptoms.

Few investigations are available of the effect of surgical treatment of gastro-oesophageal reflux on the sensitivity of the oesophagus to acid.

Skinner & Booth (1970) examined twelve patients after different reflux-preventive operations. All patients were free of symptoms, although two still had an acid-sensitive oesophagus.

Behar et al. (1974) examined ten patients before and one year after an anterior fundoplication. All had positive acid perfusion tests preoperatively. After the operation, symptoms could be provoked in two patients who still had

spontaneous symptoms. In the remaining eight patients, who were free of symptoms, no symptoms could be provoked.

Boesby (1977 (VIII)) investigated 37 patients with hiatus hernia and symptoms attributable to gastro-oesophageal reflux that indicated surgical repair (modified Bel-sey MK IV repair). Before the operation 17 patients showed positive acid perfusion tests. Three months after the operation, two patients had positive acid perfusion tests, while three asymptomatic individuals had an acid-sensitive oesophagus.

On the basis of the investigations above it can be concluded that operations to prevent gastro-oesophageal reflux are followed by a reduction of oesophageal sensitivity to acid.

5.3 Continuous pH recording in the oesophagus

The results of continuous pH recording in the oesophagus in patients with symptoms of gastro-oesophageal reflux are stated in Table I-5.

Spencer (1969), in his original work, compared the results of 18-hour continuous pH recordings in patients with hiatus hernia and symptoms of gastro-oesophageal reflux with the results from control material. The investigation showed that on an average the patients had a longer duration of pH below 4 than the control subjects. The difference was most prominent in nocturnal registration, during which the patients lay on their backs, and less prominent in daytime registration, during which the position of the patients was not restricted.

Johnson & DeMeester (1974a) used several different variables of acid reflux in 24-hour pH monitoring of controls and patients with reflux symptoms. The results of this investigation demonstrated that the duration of pH below 4 in the standing and in the supine position was longer in patients than in controls. Furthermore, they showed that the total number of reflux episodes and the number of reflux episodes of more than five minutes duration was larger for

patients than for controls, and that the duration of the most prolonged reflux episode was longer in patients than in controls.

Several later investigations have confirmed that patients with symptoms of gastro-oesophageal reflux have low pH values distally in the oesophagus of longer duration than normal subjects or asymptomatic controls (DeMeester, Johnson & Kent, 1974; DeMeester & Johnson, 1975; Boesby, 1977 (VI)); Irvin & Perez-Avila, 1977; Stanciu, Hoare & Bennett, 1977).

In the present study it was not possible to confirm that the total number of reflux episodes is larger in patients than in normal subjects (Boesby, 1977 (VI)). This may be ascribed to differences in method, as Habibulla, Ammann & Collis (1971) found that the number of reflux episodes was larger in the standing than in the supine position in patients with hiatus hernia, whereas the total duration of pH below 5 was not different. In the study by Johnson & DeMeester (1974a) a period was included where the patients were upright, whereas this was not the case in VI.

In all the investigations published there have been overlaps between the results from patient material and the results from normomaterial/controls. The degree of overlap depends, among other things, on the limits set as a criterion of acid reflux. In most investigations pH below 4 distally in the oesophagus is considered to be an indication of gastro-oesophageal reflux. pH in the oesophagus varies between 6.0 and 7.5 in normal, fasting individuals (Boesby, 1977 (III)) and the application of the duration of pH below 5 as the only criterion of reflux leads to the clearest differentiation between patients and normal subjects (Boesby, 1977 (VI); Stanciu et al., 1977). Lichter (1974) proposed that the duration of pH in the interval 1.0 to 2.3 should be used as a criterion of noxious reflux; i.e. an interval where hydrochloric acid per se is able to induce changes in the oesophagus, and where the pepsinogen/pepsin system is activated (Goldberg, Dodds, Gee, Montgomery & Zboralske,

Table I-5: Results of continuous pH recording in patients with symptoms of gastro-oesophageal reflux. In all cases the mean value is stated. Figures in brackets have been subjected to calculations (the results originally stated in minutes). N is the number of subjects included in the investigation. D is the duration of the examination in hours. Underlined figures state one standard deviation (SD). \$ states mean value -SD to mean value +SD. \$\$ states range.

Author	N	D	Duration of pH ^{<} the limits stated				Number of reflux episodes
			2.3 %	3 %	4 %	5 %	
Spencer (1969)	15	18	-	-	(24.7) (0-50.1)\$	-	-
Woodward (1970)	33	15	-	0-5.3\$\$	0-30.6\$\$	0.1-66.0\$\$	-
Habibulla et al. (1971)	20	5	-	5.8	16.7	33	9.4 <u>2.1</u>
Lichter (1974)	41	9½	-	-	0-93.3\$\$	-	-
DeMeester & Johnson (1975)	16	24	-	-	11.1 <u>4.6</u>	-	63.5 <u>26.2</u>
Atkinson & van Gelder (1977)	20	12	-	-	(9.4) (0-33)\$\$	-	-
Stanciu et al. (1977)	210	15	-	-	7.0 <u>7.7</u>	13.3 <u>12.6</u>	(13)
Boesby (1977 (VI))	59	12	2.68 0-32.34\$\$	7.23 0-60.17\$\$	15.71 0-85.0\$\$	26.32 0-96.32\$\$	15 0-120\$\$
Irvin & Perez-Avila (1977)	27	15	-	-	(9.0) (0-84.0)\$\$	(22.7) (0-86.5)\$\$	- -

1969). In his investigation the application of that criterion would bring the results of the pH examination more in line with symptomatology and endoscopic oesophagitis. In VI the application of the criterion " $\text{pH} \leq 2.3$ " did not result in a better differentiation between the groups.

Patrick (1970) used the area between pH 5 and the pH curve (2.3) as a variable and could not demonstrate any difference between patients and controls.

Several investigations have demonstrated good agreement between the results of continuous pH monitoring and the patients' symptoms (Johnson & DeMeester, 1974b; Lichter, 1974; Stanciu & Bennett, 1974b); but there does not seem to be any direct correlation between the duration of low pH and the severity of symptoms (Woodward, 1970; Atkinson & van Gelder, 1977; Boesby, 1977 (VI)).

Investigations of the relationship between endoscopic oesophagitis and results of acid reflux examinations have not given unambiguous results, since good (Lichter, 1974; Stanciu, 1975; Atkinson & van Gelder, 1977) as well as poor (Woodward, 1970; Irvin & Perez-Avila, 1977) correlations have been described. The existence of histologically verified oesophagitis seems to correlate with the results of continuous pH monitoring (Johnson & DeMeester, 1974b; Stanciu, 1975).

Several conditions may explain the results mentioned above. In situ measurement of pH in the reflux material means measurement of a single qualitative variable, and by extending the monitoring period over some time, the examination is made semiquantitative. The results of the investigation do not allow any conclusions regarding the volume of the reflux material and the area of the oesophageal mucosa in contact with the reflux material. Neither does the investigation allow conclusions regarding the content of some of the other known pathogenetic components of the reflux material, especially bile (5.2 and 5.5). However, the admixture of bile only influences the results of pH measurements

on application of the lowest limits (Henderson, Mugashe, Jeejeebhoy, Szczepanski, Cullen, Marryatt & Boszko, 1973). Individual sensitivity to acid of the oesophagus (Bennett & Atkinson, 1966) can explain the great variation of results and the overlap of different patient and control groups.

The aim of surgical treatment of gastro-oesophageal reflux and the more recent surgical procedures have been mentioned in 5.1.

In a prospective study of 21 patients with hiatus hernia and symptoms of gastro-oesophageal reflux Habibulla & Collis (1973) demonstrated that operation a.m. Collis (1968) is followed by a reduction of the duration of contact between the oesophageal mucosa and acid reflux material and by a reduction of the number of reflux episodes.

DeMeester, Johnson & Kent (1974) completed a prospective, randomized study of 45 patients with symptoms of gastro-oesophageal reflux. The aim of the study was to evaluate the efficiency of anti-reflux surgery a.m. Nissen, Hill and Belsey MK IV. The patients were clinically, radiologically and endoscopically evaluated and intraluminal oesophageal manometry, acid clearing investigations, and acid reflux studies were carried out. 24-hour continuous pH monitoring in the oesophagus was executed in 34 patients preoperatively and in 41 patients postoperatively. The results of the investigation demonstrated that all anti-reflux operations were followed by a reduction of the acid reflux tendency, and that this reduction was most prominent after the operation a.m. Nissen.

The present study (VI) includes 39 patients with hiatus hernia and symptoms attributable to gastro-oesophageal reflux, indicating surgical repair. All patients underwent 12-hour continuous pH recording in the oesophagus before and three months after a modified Belsey MK IV repair. The operation was followed by a reduction of the acid reflux tendency to values equivalent to those seen in normal sub-

jects. Of patients who became asymptomatic after surgery, some still had acid reflux above the normal upper limit. This underlines the significance of individual sensitivity of the oesophagus to acid. Patients who still had symptoms after the operation, also has significant acid reflux post-operatively.

The present study of the effect of surgical treatment on symptom-provocative acid reflux does not include any investigations with long-term observations. Decisive conclusions concerning the operation best suited for the individual patient will need years of observation in a prospective, randomized series of investigations which also include patients undergoing medical treatment.

The cause of the demonstrated reduction in the tendency to acid reflux after surgery may be an improvement of the competence of the gastro-oesophageal region. Many investigations have demonstrated that gastro-oesophageal sphincter pressure increases after operation (5.1). Postoperative changes of the composition of potential reflux material have only been investigated after operation a.m. Collis (Ward, 1970) and after a modified Belsey MK IV repair (Boesby, 1977 (IV)) (5.5). The results of continuous oesophageal pH monitoring are not independent of gastric acid secretion (6.2). The results of the pH investigations do not allow direct conclusions to be drawn concerning the efficiency of the gastro-oesophageal barrier created during the operation. It can be concluded that the operations are followed by a reduction of the duration of contact between the oesophageal mucosa and acid secretions.

5.4 The acid-clearing test

The results of the acid-clearing test in patients with symptoms of gastro-oesophageal reflux are stated in Table II-5.

In their original work, Booth, Kemmerer & Skinner (1968) examined normal subjects as well as patients with symptoms of gastro-oesophageal reflux and found that all

Table II-5: The results of acid-clearing tests in patients with symptoms of gastro-oesophageal reflux. N is the number of patients involved. SD is the standard deviation.

Author	N	pH limit	Number of swallows
Booth et al. (1968)	19	≥ 6	15 - > 40 (range)
Stanciu & Bennett (1973a)	55	≥ 5	5 - 52 (range) 16.6 (mean) 9.5 (SD)
Krejs et al. (1976)	48	≥ 6	39.6 (mean) 18.5 (SD)
Boesby (1977 (v))	57	≥ 5	5 - > 30 (range)
Miller et al. (1977)	7	≥ 6	9 - 20 (range) 15 (mean)

patients with symptoms had prolonged acid clearing. A small group of patients with hiatus hernia, but without symptoms, had normal acid clearing ability, which was also the case in patients with upper abdominal pain, but without radiologically demonstrable changes. The patients underwent investigations of gastro-oesophageal reflux by short-term pH measurements in the oesophagus parallel to reflux provocation. The results demonstrated a connection between demonstrable reflux and prolonged acid clearing.

In a later study by the same team (Skinner & Booth, 1970) a correlation was found between prolonged acid clearing on one hand and on the other the presence of hiatus hernia, symptoms of gastro-oesophageal reflux, reflux demonstrated by short-term pH measurements, positive acid perfusion tests and endoscopic oesophagitis. In this investigation there was a significant overlapping of the different groups. Only 57 of 84 patients with typical symptoms had prolonged clearing. Most later investigations have confirmed that on an average patients with symptoms have prolonged acid clearing. Nevertheless, there are overlaps of the results of the acid-clearing test in normal subjects/controls and in patients (Stanciu & Bennett, 1973a; Miller, Hogan, Dodds, Arndorfer & Stef, 1974; Krejs, Seefeld, Brändli, Bron, Caro, Schmid & Blum, 1976; Boesby, 1977 (V)).

No correlation between the results of the investigation and the severity of symptoms has been demonstrated (Boesby, 1977 (V)).

Stanciu & Bennett (1973a) found that acid clearing ability was reduced in proportion to the severity of endoscopic oesophagitic changes seen; this observation could not be confirmed by Miller et al. (1974).

One of the functions determining the duration of contact between the oesophageal mucosa and the reflux material is the ability of the oesophagus to dispose of the reflux material. In this connection it is therefore of interest that Stanciu & Bennett (1974a) were able to demonstrate a positive

correlation between the mean duration of the reflux episodes during continuous pH monitoring in the oesophagus and the results of the acid-clearing test.

The mechanism which determines the reduction of acid clearing ability in patients with symptoms of gastro-oesophageal reflux still needs to be clarified. Motility disturbances in the oesophageal body such as simultaneous contractions or peristaltic contractions with low pressure amplitudes or disorders of the sphincter relaxation may be followed by prolonged acid clearing; however, normal acid clearing ability is also seen in such patients (Stanciu & Bennett, 1973a; Boesby, 1977 (V)). Prolonged acid clearing has been seen in patients where motility disorders could not be demonstrated. This indicates that other factors, e.g. the physical state of the oesophagus, may influence acid clearing ability. Oesophagitis has been demonstrated both in patients with normal and in patients with abnormal acid clearing (Stanciu & Bennett, 1973a). It has not been possible to determine the conditions that lead to symptomatic gastro-oesophageal reflux. It may be altered motility of the oesophageal body resulting in prolonged contact between the oesophagus and the reflux material, or it may be development of massive reflux resulting in changes in the oesophagus and thus resulting in prolonged acid clearing.

Animal experiments have demonstrated that infusion of acid and bile into the oesophagus is followed by reversible disorders of the motility in the oesophagus of the same kind as those seen in patients with hiatus hernia and symptoms of gastro-oesophageal reflux (Henderson, Mugashe, Jeejeebhoy, Cullen, Boszko, Szczepanski & Marryatt, 1974). Medical treatment of gastro-oesophageal reflux is followed by an improvement of acid clearing ability, although the acid-clearing test is not normalized in all cases where patients become asymptomatic (Stanciu & Bennett, 1973a).

Acid clearing ability is improved by elevation of the upper part of the body (Stanciu & Bennett, 1973a) and in the

sitting and standing position (Krejs et al., 1976). This must be ascribed to the influence of gravity. Intravenous injection of metoclopramide (Stanciu & Bennett, 1973b) and subcutaneous injection of bethanecol (Miller, Ganeshappa, Dodds, Hogan, Barreras & Arndorfer, 1977) improve acid clearing ability. The effect may be due to improved efficiency of the peristaltic contractions of the oesophagus, since the pressure amplitude of the peristaltic contractions increases (Misiewicz & Dilawari, 1973).

Booth et al. (1968) studied six patients before and after reflux-preventive surgery. After surgery four of them had normal clearing ability, whereas two had improved clearing ability. The investigation demonstrated that acid clearing ability improved after surgical treatment of gastro-oesophageal reflux. It was not possible to confirm this observation in a later investigation (Skinner & Booth, 1970). DeMeester, Johnson & Kent (1974) could not demonstrate any significant effect of reflux-preventive surgery a.m. Hill, Nissen and Belsey MK IV on acid clearing ability. Kaunitz, Maas, Vastola & Katz (1974) studied 26 patients before and after simple reposition and fixation of a hiatus hernia. They were not able to demonstrate changes of acid clearing ability after the operation. In the present study (V) examination of 40 patients before and three months after a modified Belsey MK IV repair for hiatus hernia did not demonstrate any effect of the operation on acid clearing ability.

Patients who are asymptomatic after the above-mentioned operations may continue to have prolonged acid clearing. One of the reasons for the lack of effect of surgery on acid clearing ability may be that the reflux-induced changes in the oesophagus had not healed in the short period of observation used in the published papers. Another reason may be that the surgical procedures per se partly inhibit the emptying of the oesophagus.

Acid clearing ability is one of the components of the "reflux model" (1.2); in postoperative evaluation of pati-

ents, however, it is of minor importance, as reflux-preventive surgery is followed by termination or considerable reduction of gastro-oesophageal reflux (Habibulla & Collis, 1973; DeMeester, Johnson & Kent, 1974; DeMeester & Johnson, 1975; Boesby, 1977 (VI)).

Following medical treatment of gastro-oesophageal reflux a reduction of acid reflux is seen (Stanciu & Bennett, 1974c). This effect is not permanent (Behar, Biancani, Spiro & Storer, 1974), so an improvement of acid clearing ability in such cases must be regarded as important for the effect of the treatment.

5.5 Gastric acid secretion

In animal experiments as well as in human investigations it has been proved that the composition of the reflux material is of importance for the reaction of the oesophagus to the material (Cross & Wangensteen, 1951; Redo, Barnes & de la Sierra, 1959; Helsing, 1960; Lippa & Thal, 1966; Goldberg, Dodds, Gee, Montgomery & Zboralske 1969; Gillison, de Castro, Nyhus, Kusakari & Bombeck, 1972; Henderson, Mugashe, Jeejeebhoy, Szczepanski, Cullen, Marryatt & Boszko, 1973; Wickbom, Bushkin & Woodward, 1974; Crumplin, Stol, Murphy & Collis, 1974).

Investigations of gastric acid secretion as a step towards characterizing potential reflux material and of the importance of acid secretion for the development of symptomatic gastro-oesophageal reflux have not provided unambiguous information. Great variation in the composition of patient material and in the methods for determining acid secretory variables may account for this.

Basal acid secretion and maximal acid secretion have been measured in controls, patients with hiatus hernia, and patients with hiatus hernia and coexisting duodenal ulcer (Williams, Lawrie & Forrest, 1967). In patients with hiatus hernia and duodenal ulcer, gastric acid secretion was higher than in controls and higher than in patients with symp-

tomatic hiatus hernia without duodenal ulcer. Patients with hiatus hernia without duodenal ulcer had acid secretion which did not differ from that of the controls. This result has been confirmed in later investigations (Spencer, 1972; Csendes, Larrain & Uribe, 1974).

Silber (1969) found no relationship between the symptoms of heartburn and hypersecretion. Williams et al. (1967) could not demonstrate any relationship between increasing severity of symptoms and increasing basal or maximal gastric acid secretion. These results were confirmed in the present study (IV) and it was moreover demonstrated that the symptoms do not relate to the other variables of gastric acid secretion. Gillison & Nyhus (1971) found that maximal gastric acid secretion was lower in patients with heartburn than in patients without that symptom. They did not describe in detail the composition of the material used for the study.

Casten (1964) found that nocturnal acid secretion was higher in patients with symptomatic hiatus hernia than in patients with asymptomatic hiatus hernia. Most of the patients with symptoms had coexisting duodenal ulcer. In a group of patients with symptomatic hiatus hernia without duodenal ulcer, Stol, Murphy & Collis (1974) found that both basal acid secretion and maximal acid secretion were higher than in normal subjects. It was not possible to relate acid secretion directly to the endoscopic or symptomatic response to reflux.

Winkelstein, Wolf, Som & Marshak (1954) claimed that endoscopic and histological oesophagitis was the result of gastro-oesophageal reflux in patients with high acid output. However, Lindskog & Kline (1957) found oesophagitis in patients with low, normal and high acid secretion. Maximal acid secretion does not correlate with the degree of endoscopic (Squire, Glick & Benn, 1968; Stanciu, 1975) or histological oesophagitis (Stanciu, 1975). Csendes et al. (1974)

studied basal acid secretion and maximal acid secretion in patients with Barrett's syndrome, patients with symptomatic hiatus hernia and normal subjects. No difference between the groups could be demonstrated. In patients with benign stricture of the oesophagus basal acid secretion (Crumplin et al., 1974; Stol et al., 1974) and maximal acid secretion (Stol et al., 1974) have been shown to be higher than in normal subjects.

These investigations of the composition of potential reflux material have not led to a simple explanation of oesophageal response to reflux, and the results cannot form the basis of a rational treatment of patients with symptoms of reflux, except perhaps in the cases where symptoms and possibly stricture coexist with high acid secretion. Future investigations may show that vagotomy in conjunction with a reflux-preventive operation may have a beneficial effect in these particular patients. In a retrospective study Vansant & Baker (1976) found that vagotomy and pyloroplasty as supplements to Hill's posterior gastropexy reduced the surgical results in patients with hiatus hernia without duodenal ulcer.

Further investigations of the composition of reflux material in patients with well defined symptoms and signs will probably contribute to the understanding of the reaction of the oesophagus to reflux. The content of bile components in the potential reflux material has been investigated, but the results have not led to decisive conclusions (Crumplin et al., 1974; Kaye & Showalter, 1974b; Stol et al., 1974). Further important information can be obtained by systematic investigations of the reflux material with regard to acid content, enzymatic activity, volume and content of bile components.

The effect of a modified Belsey MK IV repair for hiatus hernia on gastric acid secretion was studied in 34 patients (Boesby, 1977 (IV)). The results of the investigation demon-

strated that the operation was followed by a rise in pH of the basal secretion, and a reduction of the volume of basal secretion and basal acid secretion. Maximal acid secretion and the volume of secretion during maximal secretion were reduced. There were no alterations of the characteristics of fasting secretion. Ward (1970) studied patients before and after surgery a.m. Collis and found a reduction of basal secretion after surgery. Analogous investigations have not been published in connection with other types of surgery.

The demonstrated changes in acid secretion were probably caused by damage to the vagus nerve during surgery. Precautions were taken to preserve the vagus nerve during the operation; however, since the nerve in the cardia region takes a varying course (Gravgaard, 1968; Skandalakis, Rowe, Gray & Androulakis, 1974) and since the surgical method used necessitates mobilisation and exposition of the whole cardia region, it was probably not possible to preserve all nervous branches. Partial denervation of the stomach is followed by similar changes in acid secretion (Konturek, Wysocki & Oleksy, 1968; Jepson, Lari, Humphrey, Smith, Wilkinson & Johnston, 1973; Nundy & Baron, 1974). In IV no clinical symptoms or radiological signs of gastric retention after the operation were found, likewise there were no alterations of the volume of fasting gastric secretion.

Giles, Clark & Buchan (1968) demonstrated that acid perfusion in the oesophagus in patients with heartburn was followed by an increase of basal gastric acid secretion. They thought that this effect was released reflexly via the vagus nerve, and they regarded the effect as part of a self-perpetuating mechanism in the development of gastro-oesophageal reflux. Ward (1970) confirmed these results and further demonstrated that operation a.m. Collis was followed by reduced gastric secretory response to acid perfusion in the oesophagus. The demonstrated changes in gastric acid secretion after surgery (Ward, 1970; Boesby, 1977 (IV)) can theoretically

be explained as modifications of the activity of the reflex chain.

The demonstrated changes of the variables of acid secretion after operations to prevent reflux are of importance not only in the clinical evaluation of the surgical results, but also in the cases where the efficiency of the surgically established gastro-oesophageal barrier is evaluated by means of pH measurements in the oesophagus. The results of pH recordings in the oesophagus are not independent of gastric acid secretion (Boesby, 1977 (VII)) (6.2). In conclusion, the demonstrated changes do not imply that acid reflux measurements cannot be used partly to evaluate surgical results, only that conclusions cannot be drawn directly from a reduction of acid reflux to an improved reflux barrier (5.3).

CHAPTER 6 RELATIONSHIPS BETWEEN THE INVESTIGATIONS

6.0 Introduction

Only a few studies have concentrated on the relationship between the various methods which have been used for the evaluation of the physiological and pathophysiological conditions in the gastro-oesophageal region. A short description of the relationships between the results of continuous pH monitoring, the basal gastro-oesophageal sphincter pressure and the variables of gastric acid secretion will be stated here.

6.1 Gastro-oesophageal acid reflux and sphincter pressure

A study of the relationship between the results of 12-hour continuous pH recording in the oesophagus and the basal gastro-oesophageal sphincter pressure is described in VII. The study included 108 sets of observations in 108 different subjects. The results demonstrated an inverse correlation between the duration of pH below 5, 4, 3 and 2.3 and

the number of reflux episodes on one hand and the basal gastro-oesophageal sphincter pressure on the other. Johnson & DeMeester (1974c) measured sphincter pressure and carried out 24-hour continuous pH recording in 87 individuals. In this study there was an inverse correlation between sphincter pressure and the results of pH monitoring (24-hour pH "score" (2.3)).

The results above support the view that the pressure in the gastro-oesophageal region is an expression of the resistance against passage from the stomach into the oesophagus (Cohen & Harris, 1970). The results are in accordance with investigations which have shown that mean basal gastro-oesophageal sphincter pressure is lower in patients with symptoms of gastro-oesophageal reflux than in asymptomatic individuals (5.1).

Variation of acid reflux can only in part be explained by variation in basal sphincter pressure (Boesby, 1977 (VII)).

As the sphincter region is not a static structure, but controlled by regulating mechanisms (1.1), the measurement of the basal pressure is only an expression of the actual strength of the region. The basal pressure does not indicate possible changes in sphincter pressure.

6.2 Gastro-oesophageal acid reflux and gastric acid secretion

The indicator of reflux during continuous pH recording in the oesophagus is the pH of the reflux material. For reflux to be registered during the investigation, the reflux material must be sufficiently acid. VII describes an investigation of correlations between the results of continuous pH monitoring and the composition of the potential reflux material.

The study demonstrated a direct correlation between the duration of pH below the limits 3, 4 and 5 and the number of reflux episodes on one hand, and the volume of basal gastric secretion on the other. This indicated that the investigation

results were dependent on the volume available for reflux, as conditions in most of the period during which pH monitoring was carried out, were more or less identical with basal conditions. The investigation also demonstrated that the duration of pH below limits 4 and 5 and the number of reflux episodes were directly correlated to the basal gastric acid secretion. This may be explained by the qualitative nature of the examination. Stanciu (1975) did not find any correlation between basal gastric acid secretion and the duration of pH below the limits 3, 4 and 5 by 15-hour pH monitoring.

Spencer (1969) demonstrated a direct correlation between maximal gastric acid secretion in patients with duodenal ulcer and the duration of low pH in the oesophagus in daytime. The material consisted of five patients. In a group of ten patients with hiatus hernia and without duodenal ulcer this correlation could not be demonstrated. Stanciu (1975) studied 72 patients and Boesby (1977 (VII)) studied 75 individuals. In these investigations no correlation between the results of the pH recording and maximal gastric acid secretion was demonstrated.

Furthermore in VII investigations were carried out regarding relationships between the results of pH monitoring and the volume, pH, acidity and total hydrogen ion content of the fasting secretion, as well as the pH and acidity of the basal secretion. No relationships were demonstrated between the variables mentioned above.

Only a minor part of the variation can be explained by the significant correlations above. However, the relationships are of importance in the cases where the pH monitoring test is used to explain the surgical results and where the operation per se induces changes in gastric acid secretion (5.3, 5.5; Boesby, 1977 (IV)).

6.3 Gastric acid secretion and basal gastro-oesophageal sphincter pressure

Investigations of relationships between the basal gastro-oesophageal sphincter pressure and gastric acid secretory variables have been used in research into the regulation of sphincter pressure under physiological and pathophysiological conditions (Pedersen, 1975d). Neither investigations in the present study (VII) nor other studies (Pedersen, 1975d) have demonstrated any relationships that could add to the understanding of the mechanisms which determine the development of gastro-oesophageal reflux or which are of importance in the interpretation of test results.

CHAPTER 7 CONCLUDING REMARKS

7.0 Introduction

As can be seen from this review, especially technical progress has made it possible to develop methods of investigation whose results can be used for objective evaluation of the physiological and pathophysiological conditions in the gastro-oesophageal region and in the lower part of the oesophagus. The individual tests elucidate some of the components that make up the "reflux model" (1.2). The methods are applicable to groups of individuals, and the results of the investigations can be used for the evaluation of such groups; however, the factors which are of importance for the development of symptomatic gastro-oesophageal reflux in the single individual still remain unclarified. The results of the investigations cannot therefore form the basis of individual treatment of patients.

7.1 Possible future investigations

The methods described can be used for objective evaluation of the effect of both medical and surgical treatment of reflux and can form the basis of selection of patients for

the necessary prospective, randomized series of investigations.

The methods of investigation can also be used to evaluate parts of the pathophysiological basis of symptom complexes which may be of oesophageal origin, e.g. x-ray negative dyspepsia and gastric or duodenal ulcers.

An extension of the research programme to include continuous registration of swallows parallel to pH monitoring in the oesophagus would add information about possible differences in the spontaneous motility response of the oesophagus to reflux. Such differences may form the basis of the development of symptomatic gastro-oesophageal reflux.

Development of a test to provoke oesophageal symptoms by using different test solutions for the perfusion of the oesophagus might contribute to the explanation of the basis of symptoms.

Development of an in situ method for determination of the bile content in the reflux material might contribute important information and would have decisive influence on future reflux studies.

If within a short span of years research into gastro-oesophageal reflux is to solve the problems still attached to the selection of patients and of treatment, several conditions must be fulfilled. Technical equipment and methods must be standardized, and definitions of symptoms and material must be made uniform. Finally, the series of treatment carried out must be well defined.

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